like peptide 1 (7-36) amide agonist delays gastric emptying" in Claims 15, 20, 25, and 30. Claims 18, 23, 28 and 33 have been amended to correct a typographical error and indicate that the glucagon-like peptide 1 (7-36) amide agonist is "glucagon-like peptide 1 (7-37)." Thus, this Response is not intended to limit, does not limit, and may not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents which should be applied to the fullest extent to protect Applicant from those who may misappropriate his invention by commercializing subject matter that is not substantially different from the claimed inventions. *See Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1521-22, 35 USPQ2d 1641, 1648 (Fed. Cir. 1995) (en banc), *rev'd on other grounds, Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 41 USPQ2d 1865 (1997). The amendments are fully supported by the application as filed and add no new matter (see, for example, pages 5-7).

Applicant responds below in detail to each of the Examiner's questions presented in the non-final Office Action mailed June 18, 1999.

I. THE ABSTRACT

In order to expedite prosecution, Applicant has added an abstract on a separate sheet (Exhibit A hereto) as requested by the Examiner. See 37 C.F.R. § 1.72(b). Applicant's submission of an abstract as requested by the Examiner is not intended to constitute, does not constitute, and may not be construed to constitute an admission against interest regarding Applicant's compliance with the patent law or any PTO Rules.

II. THE SECTION 112, FIRST PARAGRAPH, REJECTIONS

A. Written Description

Claims 18, 23, 28 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking proper description. The Examiner states that there is no specific support for the species "GLP 1 (7-36)" and suggests correcting the claims to recite "GLP 1 (7-37)."

As indicated by the Specification, the recitation of GLP 1 (7-36) rather than GLP 1 (7-37) in these claims is an obvious typographical error. See, for example, pages 2-4, and original claims 1-14. For this reason, Applicant has amended the claims as suggested by the Examiner. Thus, this issue is now moot and Applicant respectfully requests that the Examiner reconsider and

withdraw this rejection. Applicant's amendment of Claims 18, 23, 28 and 33 as requested by the Examiner to correct a typographical error is not intended to constitute, does not constitute, and may not be construed to constitute any admission against interest regarding Applicant's compliance with the patent law or any PTO Rules.

B. Enablement

Claims 15-18, 20-23, 25-28 and 30-33 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. In particular, the Examiner questions whether the specification enables "the use of any analog to GLP 1 (7-36) amide" (Paper No. 4, page 2).

With respect to peptides, the Examiner inquires whether it would involve undue experimentation to determine which amino acids in glucagon-like peptide 1 (7-36) may be changed so that glucagon-like peptide 1 (7-36) amide activity is retained:

> Claims 15-18, 20-23, 25-28 and 30-33 recite the use of an analogue to GLP 1 (7-36) amide or GLP 1 (7-36) to treat Type I diabetes; however, the present specification fails to disclose any other peptide which has GLP 1 (7-36) amide or GLP 1 (7-37) activity in treating diabetes. In addition, the specification provides no guidance as to which of the 30 amino acids may be changed while GLP 1 (7-36) amide activity is retained. The total number of 30 amino acids is 3.4×10^{29}. The number of single amino acid substitutions is 600. Because of this lack of guidance, the extended experimentation that

> would be required to determine which substitutions would be acceptable to retain GLP 1 (7-36) amide or GLP 1 (7-37) activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al., (V), newly cited, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495:), it would require an undue amount of experimentation for one of skill in the art to arrive at the other $3.4x10^{29}$ peptides that have GLP 1 (7-36) amide or GLP 1 (7-37) activity [Paper No. 4, page 2].

Applicant respectfully traverses the rejection to the extent that it may be held to apply to the present claims.

Importantly, Applicant notes that neither the rejected claims nor the present claims recite the use of "any analog to GLP 1 (7-36) amide," as indicated by the Examiner's rejection. The rejected claims recite the use of "glucagon-like peptide 1 (7-36) amide agonist[s]." The present claims recite the use of a "glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying."

In order to enable a claimed invention, all that is required is to provide sufficient information that one skilled in the art can make and use the claimed

invention. Thus, it is the law that an applicant need not describe every possible embodiment in order to obtain claims that would fully protect his or her invention. The PTO has itself recognized that limiting an applicant to the preferred materials in the absence of limiting prior art does not serve the constitutional purpose of promoting the progress in the useful arts. M.P.E.P. § 2164.08(c).

Indeed, the concerns raised by the PTO in the Paper No. 4 Office Action are of the type that were long ago rejected by the PTO's reviewing court in *In re Fuetterer*, 138 USPQ 217 (CCPA 1963) (Rich, J.). There, speaking through Judge Giles S. Rich, co-author of the 1952 Patent Act and 43-year member of the CCPA and the Court of Appeals for the Federal Circuit, the court considered an appeal from a rejection of claims to a rubber stock for producing tire treads. The claimed rubber stock included "an inorganic salt" that was defined only by the fact that it was to be "capable of holding a mixture of [a previously referred to] carbohydrate and [a previously referred to] protein in colloidal suspension in water." *Id.* at 219. The Board had affirmed the rejection of the claim as "unduly broad." According to the Board, "Since the alleged novelty appears to reside in the result

desired to be obtained by the salts, it is not proper to define the salt by what it is supposed to do rather than what it does." *Id.* at 221.

Judge Rich promptly disposed of this rejection as unsound:

> The desired result of appellant's invention is limiting the skidding of a tire tread stock on a wet surface. Appellant, in the claims before us, is not claiming this result. A myriad of alternative means for achieving this result can be easily thought of which would not require the particular combination of substances claimed by appellant. Insofar, therefore, as a "functional" claim may mean one which covers all means of arriving at the desired result, although the means by which such result is obtained is entirely different from that disclosed by the applicant, it is apparent that appellant's claims are not "functional."

Id. at 221 (emphasis added). Similarly, the result to be achieved by the use of the invention claimed by Applicant in this case is the treatment of Type 1 diabetes. Plainly other means for treating Type 1 diabetes are available that do not require the particular means claimed by Applicant (e.g., the use of insulin).

It is well settled, furthermore, that patent applicants are not required to disclose every species that may be encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). Indeed, it is not even

required that every embodiment in a disclosure be operative in order to be enabling under 35 USC 112, first paragraph. *Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *In re Geerdes*, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

Judge Rich also stressed in *In re Fuetterer* that patent applicants must be able to obtain claims that adequately protect their inventions, even though some experimentation may be required to determine if a product or method falls within the scope of the claim. Judge Rich described Fuetterer's claim and the PTO rejection as follows:

> The rejection of the claims for "undue breadth" places particular emphasis on (1) an alleged "undue burden upon the public to determine what salts are suitable for obtaining the desired results" (emphasis ours), and (2) an alleged "undue [amount of] experimentation" required of those skilled in the art to determine those salts possessing the "function asserted" by the instant claims. The undue breadth rejection phase of the instant case appears in the following posture. Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function. The examiner and the board, believing that not all inorganic salts are capable of performing this function and that one skilled in the art would not know offhand which inorganic salts are capable of so functioning, have rejected the claims as "unduly broad."

Id. at 222-223 (emphasis added). According to Judge Rich, however, this was all "beside the point" and could not support the PTO's rejection:

> We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination.

Id. at 223 (emphasis added). Likewise, Applicant's invention in this case is not the discovery that certain compounds have glucagon-like peptide 1 (7-36) amide activity, but that such compounds will be useful in the treatment of people with Type 1 diabetes.

In *In re Fuetterer*, Judge Rich further emphasized that an applicant's claims may not be restricted so that they are easily avoided simply by identifying an undisclosed compound that will work:

> If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his

> disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant.

Id. (emphasis added). Similarly, if others in the future discover other glucagon-like peptide 1 agonists aside from those set out in Applicant's specification with the ability to slow gastric emptying and treat Type 1 diabetics, Applicant will have no control over them per se (if the claims are limited to the subject matter the Examiner has indicated is enabled). Nevertheless, following *In re Fuetterer*, it is plain that under the law Applicant's claims cannot be so restricted by the PTO that they can be avoided merely by using some compound not named in his disclosure.

The claims, as amended, recite methods of treating Type I diabetes by administering a glucagon-like peptide 1 amide agonist that delays gastric emptying. Here, there is no evidence that those skilled in the art could not readily make or test known or later-developed glucagon-like peptide 1 (7-36) amide agonists for their ability to delay gastric emptying and determine their suitability for the treatment of people with Type I diabetes. *See, e.g.*, International Patent Publication No. WO 91/11457, attached hereto as Exhibit B, which

describes various glucagon-like peptide 1 peptide analogs (see page 4, line 33 - page 7, line 2) and International Publication No. WO 90/11296 attached hereto as Exhibit C, which describes various derivatives of glucagon-like peptide (See Summary of the Invention pages 5-7). There is no reason to believe that those skilled in the art could not test these and other glucagon-like peptide 1 (7-36) amide agonist compounds to evaluate their activity for the use in treating Type I diabetes patients. In view of the cases cited above, it would be improper to limit Applicant to use of preferred materials when such claims might be attempted to be avoided merely by using different agonists that could be readily made and tested given the information in the present application.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

III. THE PROVISIONAL DOUBLE PATENTING REJECTION

Claims 15-34 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 38-47 of copending Application No. 08/737,446 in view of WO 93/18786.

Applicant respectfully requests that the Examiner hold this matter in abeyance until claims in at least one application have been allowed.

IV. THE SECTION 103 REJECTIONS

Claims 15-17, 19-22, 24-27, 29-32 and 34 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Gutniak *et al.* in view of U.S. Patent No. 5,424,286, D'Alessio *et al.*, and WO 93/18786. The Examiner stated:

> One of ordinary skill in the art at the time the invention was made would have been motivated to treat Type I diabetics with GLP-1 (7-36) amide and insulin because GLP-1 decreased the need for insulin co-administration to maintain euglycemia as taught by Gutniak et al., and the glucose dependent activity of GLP-1 is a very desirable characteristic for a therapeutic agent that can be used to treat diabetes mellitus avoiding the complications of hypoglycemic side effects, as taught by the '286 patent and administer GLP-1 by an oral or nasal route since the '786 patent teaches that nasal application of GLP-1 is particularly advantageous from a patient compliance point of view and that GLP-1 oral administration is preferred in instances where extent and kinetics of absorption is not a critical issue. The results of the Gutniak et al., teachings, when viewed from the point of view of those skilled in the art (i.e. the '286 patent and D'Alessio et al.) would reasonably motivate one of skill in the art to treat Type I diabetics with GLP-1 (7-36) amide and insulin with a reasonable expectation of success. From the teachings of the references, it is apparent that one of ordinary skill in the art would

> have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references [Paper No. 4, page 5].

Applicant respectfully traverses to the extent the rejection may be held to apply to the claims as amended.

A. No Motivation To Use Compounds To Treat Type I Diabetes

Contrary to the Examiner's assertions, one of ordinary skill in the art at the time the invention was made plainly would not have been motivated to treat Type I diabetes with either glucagon-like peptide 1 (7-36) amide or glucagon-like peptide 1 (7-37). Although glucagon-like peptide 1 (7-36) amide and glucagon-like peptide 1 (7-37) were known to show insulinotropic effects *in vivo*, this does not support the Examiner's conclusion that one of ordinary skill in the art could have been motivated to treat Type I diabetes with these compounds. In Type I diabetes, insulin is deficient or completely lacking by virtue of the destruction of the patient's pancreatic beta cells (the cells that produce insulin). Thus, it would have been completely unexpected that an agent which was believed to be useful only because of its ability to potentiate insulin release could be useful in the treatment of people with Type I

diabetes, who do not have the ability to produce sufficient insulin and who have no secretory response for glucagon-like peptide 1 (7-36) amide to amplify.

Indeed, the authors of Gutniak, *et al.* support this conclusion - and do not support the Examiner's rationale - for they remarked only that glucagon-like peptide 1 (7-36) amide may be useful in the treatment of patients with NIDDM (Type II diabetes mellitus) (Gutniak *et al.*, Abstract). They said nothing about the treatment of other kinds of patients and thus recognized that their data did not support the use of GLP-1 (7-36) amide for the treatment of Type I diabetes mellitus (IDDM). Their paper concluded, for example, only that:

> A better treatment for patients with NIDDM ["Non-Insulin Dependent" (or "Type 2") Diabetes Mellitus] who do not respond to sulfonylurea therapy would be one that decreases their requirement for insulin and therefore decreased the occurrence of hypoglycemia. Our study demonstrates that at least in the short term, the administration of GLIP decreases postprandial insulin requirements and plasma insulin concentrations in patients with NIDDM. Therefore, the peptide may have a role in the treatment of some patients with diabetes.

Gutniak *et al.*, at page 1321 (emphasis added). The treatment of Type I diabetes is neither disclosed under § 102 or suggested within the meaning of § 103, and, meaningfully, is not even mentioned in either the summary

of, or the conclusion to the Gutniak *et al.* paper. Accordingly, the Examiner's remarks regarding the alleged suggested treatment of Type 1 diabetes with GLP-1 are not only without support, but are unambiguously countered by the words of the Gutniak *et al.* article - the heart of the Examiner's 103 rejection.

B. The Cited Documents Teach Away From The Claimed Invention

The Examiner appears, furthermore, to be relying on only select portions of the Gutniak *et al.* article and other cited documents in making a rejection, while ignoring other portions of the article and the other citations which do not support the Examiner's position. This is impermissible under the patent laws. *See, e.g., In re Wesslau*, 147 USPQ 391,393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.")

Applicant notes that the PTO must consider the cited documents in their entirety, including disclosures that teach away from the invention. For example, the

Examiner's rejection and statement that the Gutniak *et al.* article would suggest treatment of Type I diabetic patients is not consistent with - and cannot be reconciled to - International Patent Application WO 93/18786 ("the '786 application"), which was also cited by the Examiner. The '786 application names the lead author of the Gutniak *et al.* article, Mark Gutniak, as an inventor. According to Gutniak himself, as set forth in the '786 application, the "broadest aspect" of the invention is said to relate to the preparation of a medicament for use in the treatment of Type II diabetes. Page 4, lines 28-page 5, line 8. Thus, the primary author of the Gutniak *et al.* article independently corroborates the lack of any suggestion to treat people with Type I diabetes.

Other patent applications also describe glucagon-like peptide 1 analogs only in relation to treatment of Type II diabetes, and fail to suggest treatment of patients with Type I diabetes mellitus. *See, e.g.*, International Patent Publication No. WO 91/11457 (Exhibit B) and European Patent Application EP 0708 179 A3, attached hereto as Exhibit D. Plainly, those skilled in the art would have been, and were, led away from use of such compounds to treat Type I diabetes.

C. No Teaching Or Suggestion Of Use Of An Agonist That Delays Gastric Emptying

As noted above, the claims as amended recite methods for treating Type I diabetes by administering a glucagon-like peptide 1 amide agonist that delays gastric emptying. None of the cited documents, either alone or in combination (even though Applicant does not admit such combination is proper), teach or suggest the use of glucagon-like peptide 1 amide agonists that delay gastric emptying as presently claimed to treat Type I diabetes.

D. The '286 Patent Would Not Be Accepted By One of Ordinary Skill in the Art

Neither the '286 patent nor the D'Alessio article supply what the Gutniak *et al.* article lacks. In contrast to the Examiner's assertions, the results of Gutniak *et al.*, when viewed from the point of view of those skilled in the art, would not reasonably suggest treating Type I diabetes with glucagon-like peptide 1 (7-36) amide or glucagon-like peptide 1 (7-37). As noted above, the discussion of Gutniak *et al.* in the '286 patent must be read in light of the entire Gutniak, *et al.* article and the entire '286 patent. When it is read in this manner, it is apparent that the Examiner's reading of the '286 patent mischaracterizes Gutniak *et al.*

The statement in the '286 patent that, "[Gutniak *et al.*] reasoned that since GLIP is the naturally active form found in humans after a meal, this peptide may aid in glucose regulation in IDDM and NIDDM," is not accurate. As explained in detail above, Gutniak *et al.* concluded only that glucagon-like peptide 1 (7-36) amide may be useful in the treatment of patients with NIDDM (Type II diabetes mellitus) and did not suggest that glucagon-like peptide 1 (7-36) amide could be used to treat patients with IDDM (Type I diabetes mellitus). Thus, the Examiner's reliance on the '286 patent is misplaced. The Gutniak *et al.* article does not contain any such statement. The '286 patent, additionally, is not seen as containing any disclosure of the use of glucagon-like peptide 1 (7-36) amide agonists that delay gastric emptying for use in treating people with Type 1 diabetes.

D. The D'Alessio Article Would Not Be Accepted By One Of Ordinary Skill In The Art

Nor does the D'Alessio article support the Examiner's assertions. As noted above, both the entire D'Alessio article and the entire Gutniak *et al.* article must be considered when examining the statements in the Introduction and Abstract of the D'Alessio article to

which the Examiner has referred. For example, after the language quoted by the Examiner, the D'Alessio article points out some of the deficiencies of the Gutniak *et al.* work:

> It has recently been reported that infusions of GLP-1 into diabetic subjects decreased the insulin dosage required to maintain euglycemia. Furthermore, type I diabetic subjects treated with GLP-1 during one step euglycemic, hyperinsulinemic clamps had 10-15% higher rates of glucose than during control studies, thereby suggesting that GLP-1 may promote glucose uptake in addition to augmenting insulin release. <u>However, it cannot be determined from these data whether GLP-1 exerts an effect on insulin sensitivity, or if it promotes insulin-independent glucose disposition. Furthermore, because glucose disposal rates were studied only in diabetic subjects, it is not known whether their augmentation by GLP-1 occurs in healthy people, and this might comprise a physiologic response of the peptide.</u>

D'Alessio at page 2263, column 2, first full paragraph (emphasis added). Again, furthermore, D'Alessio is not seen to include any disclosure of the use of glucagon-like peptide 1 (7-36) amide agonists that delay gastric emptying for use in treating people with Type 1 diabetes. Additionally, even if it were true that glucagon-like peptide 1 (7-36) amide had an effect on "insulin sensitivity," which is understood not to be the case, its administration into people, *e.g.*, Type 1 diabetics who lack insulin would be of no consequence in this regard.

F. The '786 Application Adds Nothing Of Substance

The '786 application fails to cure the above defects. The fact that the '786 application states that GLP-1 related peptides can be delivered by nasal administration is beside the point. As noted above, the '786 application actually teaches away from the present invention by stating that the broadest aspect of the invention described in the '786 application related to preparation of a medicament for treatment of a patient with Type II diabetes.

In summary, it is clear that when each of the items cited by the Examiner is considered as a whole, the Gutniak *et al.* article, either alone or in combination with the '286 patent, the D'Alessio article and/or the '786 application, neither discloses nor suggests the presently claimed compositions and methods. Applicants thus request that this rejection be reconsidered and withdrawn.

CONCLUSION

For the foregoing reasons, Applicant submits that the pending claims are in condition for allowance and seek an early Notice thereof. Should any issues or

questions remain, the Examiner is encouraged to telephone the undersigned so that they may be promptly resolved.

Applicant hereby petitions for a three-month extension of time pursuant to 37 C.F.R. § 1.136. Enclosed is our check in the amount of $435.00 for a two-month extension of time. If this amount is incorrect, please charge or Deposit Account 12-2475 for the appropriate amount.

Respectfully submitted,

Dated: 12/20/99

By _____
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